

# REMARKS

Reconsideration is requested in view of the foregoing amendments, the Declaration Under Rule 132 being submitted herewith, and the following remarks.

On October 13, 1988 a "Petition and Amendment Under Rule 48," together with other related documents were filed in this patent application, seeking to have the name of Charles R. Connell added as a joint inventor. We find no acknowledgement regarding receipt of these papers or any discussion of their disposition in the Office Action. Clarification is requested.

The claims are 1 to 30.

Claims 23-30 are non-elected. Applicants again traverse the restriction requirement, inasmuch as it appears that the same search, and the same ground will be covered in the process of the examination of each set of claims. Applicants fail to see any benefit to the Patent and Trademark Office or to the public in this restriction requirement. Obviously, the Examiner has great latitude in this area. However, we submit that the proper exercise of discretion mandates the examination of all of these claims in a single patent application. Withdrawal of the restriction requirement is requested.

There is no rejection or discussion of claims 15 to 22 in the Office Action. Presumably, these claims are allowed. ✓

The typographical errors have been corrected.

The status of the parent and earlier filed patent applications referred to in the Specification has been provided.

A revised first sheet of drawings has been provided to change the "C" to --G-- in the DNA number 11 from the '5 end.

Claims 1 to 14 were rejected and the Specification objected to under 35 USC 112, first paragraph.

Preliminarily, we note that United States Patent Applications Serial No. 565,011, filed December 20, 1983 and Serial No. 709,579, filed March 8, 1985 have both been abandoned in favor of Serial No. 878,045, filed June 24, 1986, and now issued as U. S. Patent No. 4,849,513. These three prior patent applications illustrate at great length the covalent attachment of fluorescent dyes and other detectable moieties to oligonucleotides. See, for example, U. S. Patent No. 4,849,513 at column 52, line 42.

The Examiner argues that the Specification is enabling "for only four fluorophores." The fact is that the Specification is illustrative only and it enables the use of a wide range of fluorophores having highly resolvable extinction coefficients which can be selected by those skilled in the art by routine experimentation. The use of fluorophores per se for purposes of detection of small chemical moieties and fragments was not new. The novelty resides in the use of the fluorophores to label DNA fragments to permit their detection by automated means, as is discussed below, to make it possible for the first time to consider the sequencing of the complete genome. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986) at page 94:

"Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, Raytheon Co. v. Roper Corp., 724 F.2d 951,960, 220USPQ 592, 599 (Fed. Cir. 1983), is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive."

In Hybritech, one of the claimed features was the use of two monoclonal antibodies having an affinity of  $10^8$  which would react with different isotopes on the same antigen. The patent did not specifically disclose the screening of monoclonal antibodies for non-interfering pairs, nor did it disclose the procedure used to measure the affinity constant. However, enablement was found based on the fact that screening and affinity measurements were known to those skilled in the art. Furthermore, a patent need not teach, and preferably omits, what is known elsewhere in the art. Lindemann Maschinenfabrik v. American Hoist & Derrick, Co., 221 USPQ at 481, 489.

Also, Christianson v. Colt Indus. Oper. Corp., 822 F.2d 1544, 3 USPQ2d 1241 (Fed.Cir. 1987).

In United States v. Teletronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), the defendant urged that the scope of the protection must bear a reasonable relationship to the scope of enablement, and that while the specification was enabling only for the use of stainless steel electrodes, the claims were not limited in the types of materials that could be employed for electrodes. In finding a lack of enablement, the district court emphasized the

time and cost of doing certain studies that would be necessary for materials other than stainless steel. In reversing, the Federal Circuit held that such factors may be taken into account, but they did not establish that the necessary experimentation would be excessive.

The key word is "undue" not "experimentations." the term "undue experimentation" does not appear in the statute. Whether undue experimentation is required is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. Factors to be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the states of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims, In re Wands, 858 F.2d 731, 8 USPQ2d 1302 (Fed. Cir. 1988).

In the instant case, we have provided in the Specification actual specific examples of fluorophores which serve as a clear guide to those skilled in the art who wish to practice the invention with other fluorophores or chromophores having similar characteristics.

The cited MPEP 706.03 (n) and (z) are not to the contrary. These two MPEP paragraphs entitled "Correspondence of Claim and Disclosure" and "Undue Breadth," respectively, endeavor to

summarize, in very general terms, the case law regarding "enablement" under Section 112. We have analyzed the leading and most relevant case law hereinafter.

The present disclosure is more than adequate. The objection to the Specification and the related rejection of the claims should be withdrawn.

Claims 1 to 6 were rejected over Kaplan et al., U. S. Patent No. 4,318,846, and Maxam and Gilbert as disclosed in the instant Specification at page 3, in view of Khanna et al., U. S. Patent No. 4,151,065.

As the Examiner is no doubt aware, the analysis of DNA structure and its relation to gene expression has been markedly facilitated by the development of techniques for the sequencing of DNA molecules. The chemical cleavage method devised by Maxam and Gilbert started with a DNA that is labeled at one end of one strand with  $^{32}\text{P}$ . Polynucleotide kinase is usually used to add  $^{32}\text{P}$  at the 5'-hydroxyl terminus. The labeled DNA is then broken preferentially at one of the four nucleotides. The conditions are chosen so that an average of one break is made per chain. In the reaction mixture for a given base, then, each broken chain yields a radioactive fragment extending from the  $^{32}\text{P}$  label to one of the positions of that base, and such fragments are produced for every position of the base. For example, if the sequence is



the radioactive fragments produced by specific cleavage on the 5' side of each of the four bases would be:

Cleavage at A:	$^{32}\text{P-GCT}$ $^{32}\text{P-GCTACGT}$
Cleavage at G:	$^{32}\text{P-GCTAC}$
Cleavage at C:	$^{32}\text{P-G}$ $^{32}\text{P-GCTA}$
Cleavage at T:	$^{32}\text{P-GC}$ $^{32}\text{P-GCTACG}$

The fragments in each mixture are then separated by polyacrylamidegel electrophoresis, which can resolve DNA molecules differing in length by just one nucleotide. The next step is to look at an autoradiogram of this gel.

DNA can also be sequenced by generating fragments through the controlled interruption of enzymatic replication, a method developed by Sanger and his associates. DNA polymerase I is used to copy a particular sequence of a single-stranded DNA. The synthesis is primed by a complementary fragment, which may be obtained from a restriction enzyme digest or synthesized chemical. In addition to the four deoxyribonucleoside triphosphates (radioactively labeled), the incubation mixture contains a 2',3'-dideoxy analog of one of them. The incorporation of this analog blocks further growth of the new chain because it lacks the 3'-hydroxyl terminus needed to form the next phosphodiester bond. Hence, fragments of various lengths are produced in which the dideoxy analog is at the 3' end. Four such sets of chain-terminated fragments (one for each dideoxy analog) are then electrophoresed, and base sequence of the new DNA is read from the autoradiogram of the four lanes.

About  $5 \times 10^6$  bases of DNA have been sequenced in laboratories around the world since the introduction of the Maxam-Gilbert and Sanger methods. All of these studies have used autoradiographic images of gels to ascertain the lengths of DNA fragments generated by chemical cleavage and controlled interruption of replication.

According to this invention, an important and major advance in both the Maxam and Gilbert and Sanger methods have been achieved. In the new and improved methods based on Maxam and Gilbert chemistry, the end of the piece of DNA whose sequence is to be determined must be labeled. This has previously been done enzymatically using radioactive nucleosides. In order to use the Maxam/Gilbert method in conjunction with the dye detection scheme described in this invention, the DNA piece is labeled with fluorescent or colored dyes. One manner in which this may be accomplished is shown in Figure 1. Certain restriction endonucleases generate what is known as a 3' overhang as the product of DNA cleavage. These enzymes generate a "sticky end," a short stretch of single stranded DNA at the end of a piece of double stranded DNA. This region will anneal with a complementary stretch of DNA, which may be covalently joined to the duplex DNA with the enzyme ligase. In this manner one of the strands is covalently linked to a detectable moiety. This moiety may be a dye, or an amino group or a protected amino group (which could be deprotected and reacted with dye subsequent to the chemical reactions).

In using the Sanger dideoxy chemistry according to this invention, a fluorescent or colored tag is attached to the oligonucleotide primer - a differently colored one in each of the four chain-terminating reaction mixtures (e.g., a blue emitter for termination at A and a red one for termination at C). In both of the methods the reaction mixtures are combined and electrophoresed together. The separated bands of DNA are then detected by their fluorescence as they pass out the bottom of the tube, and the sequence of their colors directly yields the base sequence. A major result of this fluorescence detection method is that it can readily be automated. The sequencing of the entire E.coli genome ( $3 \times 10^6$  base pairs) has now become feasible. This invention has made it possible to begin to think about determining the sequence of extensive stretches of the human genome, which contains  $3 \times 10^9$  base pairs. The prior art method using autoradiograms requires contact with the gel and is too slow to enable full scale analysis of the human genome.

Kaplan et al pertains to a horizontal slab gel electrophoresis apparatus. The Examiner refers to Kaplan et al. at column 3, lines 5 to 10 which states:

"Yet another object of the present invention is to provide a horizontal slab gel electrophoresis apparatus in which a removable tray is constructed of an ultraviolet transmitting material to permit viewing of the gel through the removable tray."

Khanna et al. disclose a class of di(chalcogen ether) symmetrically substituted fluorescein compounds which are disclosed, column 2, line 45, to be useful when conjugated to polypeptides or to solid or soluble supports for use in diagnostic immunoassays. Neither of these patents is at all pertinent to the present invention and suggest nothing at all in relation to the DNA sequencing. Basically, Kaplan et al. and Khanna et al. logically add nothing to Maxam & Gilbert (or Sanger).

The present invention represents a major advance in the art of DNA sequencing. The proper approach to the obviousness issue must start with the claimed invention as a whole. Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1448 [223 USPQ 603, 609-10] (Fed. Cir. 1984). The invention as a whole embraces the structure, its properties and the problem it solves. In re Wright, 848 F.2d 1216, 1219 [6 USPQ2d 1959, 1961-62] (Fed. Cir. 1988). The determination of whether a novel structure is or is not "obvious" requires cognizance of the properties of that structure and the problem which it solves, viewed in light of the teachings of the prior art. Id.

An invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d at 1448 [223 USPQ at 609]; Reiner v. I. Leon Co., 285 F.2d 501, 503 [128 USPQ 25, 27] (2d Cir. 1960). Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art.

United States v. Adams, 383 U.S. 39, 50 [148 USPQ 479,483] (1966). The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1558 [225 USPQ 26, 31] (Fed. Cir. 1985). (emphasis in original), citing Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462 [221 USPQ 481, 488] (Fed. Cir. 1984). In other words, obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." In re Fine, 837 F.2d 1071, 1075 [5 USPQ2d 1596, 1599] (Fed. Cir. 1988), quoting ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577 [221 USPQ 929, 933] (Fed. Cir. 1984).

Whether a particular combination might be "obvious to try" is not a legitimate test of patentability. Id. However, the meaning of this maxim is sometimes lost since "[a]ny invention that would in fact have been obvious under Sec. 103 would also have been, in a sense, obvious to try." In re O'Farrell, 853 F.2d 894, 903 [7 USPQ2d 1673, 1680-81] (Fed. Cir. 1988). the admonition that "obvious to try" is not the standard under Sec. 103 has been directed mainly to the following situations: (1) where what was "obvious to try" would have been to vary all parameters to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of

many possible choices is likely to be successful; and (2) where what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. Id.

"A patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified." In re Spinnoble, 405 F.2d 578, 585 [160 USPQ 237, 243] (C.C.P.A. 1969).

The sequencing of large genomic segments has presented a daunting challenge to those skilled in the art. This problem has been solved by the present invention.

We submit herewith the Declaration Under Rule 132 by Elgin Edwards, establishing the commercial success of this invention.

In the landmark case on obviousness, Graham v. John Deere, 383 U.S. 1 [148 USPQ 459] (1966), the Supreme Court articulated the following test:

"Under Sec. 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the

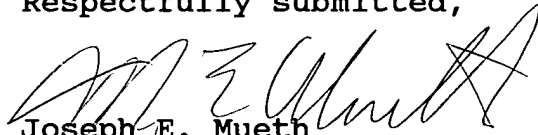
circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."

The present invention clearly satisfies the requirements for a finding of non-obviousness.

The rejection of claims 1 to 6 should be withdrawn.

In the absence of more pertinent prior art, the Notice of allowance is requested.

Respectfully submitted,

  
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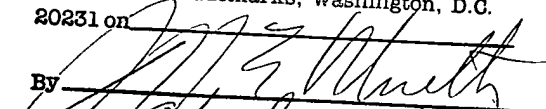
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